REMARKS

I Amendment to the Specification

As requested by Examiner, reaction schemes on pages 42, 44 and 48 are replaced with corrected schemes. The Examiner also points out that the amendment filed on February 19, 2002 regarding "Brief Description of the figures" has not been entered. Applicants have likewise cancelled that amendment in this response to ensure the record is clear. The three structures on the bottom of page 14 and the structure on top of page 15 have been replaced so that the double bonds in the imidazole rings are properly drawn to render the positively charged nitrogen atoms tetravalent. The graphs on pages 53, 57, 58, 59, and 60 have been deleted from the specification and presented as Figures 1A and 1B, 2, 3, 4A, and 4B respectively. In addition, the references to these graphs in Examples 27 (page 52) and 32 (page 55), and in Comparative Example 1 (page 59) are amended to indicate the appropriate figures. Also, the "Brief Description of the Figures" is added to page 7 before "Details Description of the Invention." No new matter is added by these amendments. A marked-up version of the changes in the specification is included in the "**Version With Markings To Show Change Made**" in Appendix A. Clean copies of the Figures with drawing labels are included in Appendix B.

II Status of the Claims

Claims 1-3, 6-10, 18, 24-27, 30-34, 44 and 46 are pending. Claims 1, 24 and 25 are amended by adding the phrase "water-soluble" before "linear cyclodextrin copolymer." Water soluble cyclodextrin copolymers are disclosed in the examples where they are lyophilized from aqueous fractions. *See* Example 5 (page 31, line 27), Example 7 (page 32, line 13), Example 8 (page 32, line 21), Example 10 (page 33, line 17), Example 12, (page 35, line 1), Example 14 (page 36, line 15), Example 15 (page 38, line 4), and Example 16 (page 39, line 1). Claim 25 has also been amended to correct punctuation. No new matter has been added. Attached hereto at the end of this Amendment is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version With Markings To**

Show Changes Made" in Appendix A. As suggested by the Examiner, all the pending claims are presented in Appendix C.

III Rejections Under 35 U.S.C. §112

Claim 25 is rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter. As a result of this amendment, the terminal punctuation in line 3 has been removed and the terminal punctuation in line 5 are addeded. Therefore, Applicants respectfully request that the rejection of claim 25 under 35 U.S.C. §112, second paragraph be withdrawn.

Claims 1-3, 6-10, 18, 24-27, 30-34, 44 and 46 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification. The Examiner indicates this rejection has been reported in view of the prior art rejection over Kosak. Applicants have filed a declaration under 37 C.F.R. § 1.131 to remove Kosak as a reference against the pending claims (see below). Applicants respectfully traverse this rejection for the reasons discussed in the Responses to Office Action filed on August 1, 2001 (*see* pages 12-14) and October 18, 2001. In those responses the claims are directed to linear cyclodextrin copolymers having a repeating unit of formula Ia, Ib or a combination thereof. In addition, claims that were drawn to linear cyclodextrin copolymers having ring opened and oxidized cyclodextrin monomers were canceled according to Examiner's suggestion. Following these responses, a Notice of Allowability was mailed on November 16, 2001. Therefore, Applicants respectfully request that the rejection of claims 1-3, 6-10, 18, 24-27, 30-34, 44 and 46 under 35 U.S.C. §112, second paragraph be withdrawn.

IV Rejection Under the Doctrine of Obviousness-Type Double Patenting

Claims 1-3, 6-10, 18 and 44 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 19-23 and 45 of copending Application No. 09/203,556. According to the Examiner, although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter of the '556 application is so broadly and indefinitely defined that some, if not all, of the subject matter of the instant application is included within the vast scope of the '556 claims.

The claims of the instant invention relates to water-soluble, linear cyclodextrin copolymer comprising repeating units of the formula Ia, Ib or a combination thereof. The '556 claims relate to a composition comprising: (A) a water-soluble, linear cyclodextrin copolymer having units represented by formula Ia, Ib or a combination thereof, and (B) a water-soluble, linear oxidized cyclodextrin copolymer having units represented by formula VIa, VIb, or a combination thereof. Applicants respectfully request this rejection be withdrawn for the reasons of record or held in abeyance until the indication of allowed claims in one or both of these applications.

V Rejections Under 35 U.S.C. § 102(e) and § 103 Over Kosak

Claims 1-3, 7-10, 18, 24-27, 31-32, 44 and 46 are rejected under 35 U.S.C. § 102(e) as being anticipated by, or alternatively under 35 U.S.C. §103(a) as being unpatentable over Kosak '736 (PTO-892 ref. F). Applicants are filing a declaration under 37 C.F.R. §1.131 with this Amendment and Response. The Kosak patent was filed as application serial no. 09/223,055 on December 30, 1998, which is a continuation-in-part of application serial no. 09/067,921, filed April 29, 1998. As stated in the Declaration Under 37 C.F.R. § 1.131 and shown by the attached research report, Applicants' claimed invention was invented prior to April 29, 1998, the earliest filing date for the Kosak patent. Therefore Applicants respectfully request that the rejection of claims 1-3, 7-10, 18, 24-27, 31-32, 44 and 46 are rejected under 35 U.S.C. § 102(e) as being anticipated by, or alternatively under 35 U.S.C. §103(a) as being unpatentable over Kosak '736 be withdrawn.

VI Objection to Claims 30 and 33-34

Claims 30, 33-34 are objected to as being dependent on a rejected base claim, but would be allowable if re-written in independent form including all of the limitations of the base claim and any intervening claims and/or amended to overcome rejections under 35 U.S.C. §112. Applicants appreciate this indication of allowability. Here, claim 30 is dependent on claim 24. Both claims 33 and 34 are dependent on claim 32, which in turn is dependent on claim 25, and in turn is dependent on 24. In addition to the amendment of claims 24, and 25, the arguments presented in this Response will remove all rejection involving 24, 25, and 32. Therefore, Applicants respectfully request that the objection of claims 30, 33-34 be withdrawn.

VII Conclusion

Applicants respectfully request reconsideration of the subject application in view of the above remarks. The subject application is now in condition for allowance and early notice to that effect is respectfully solicited.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully submitted,

MORGAN, LEWIS & BOCKIUS LLP

By: _____
Jeffrey A. Lindeman
Reg. No. 34,658

Dated: May 2, 2002

Customer No. 009629
MORGAN, LEWIS & BOCKIUS LLP
1111 Pennsylvania Avenue, N.W.
Washington, D.C. 20004
(202) 739-3000; Fax: (202) 739-3001

Appendix A

Version With Markings To Show Changes Made

IN THE SPECIFICATION:

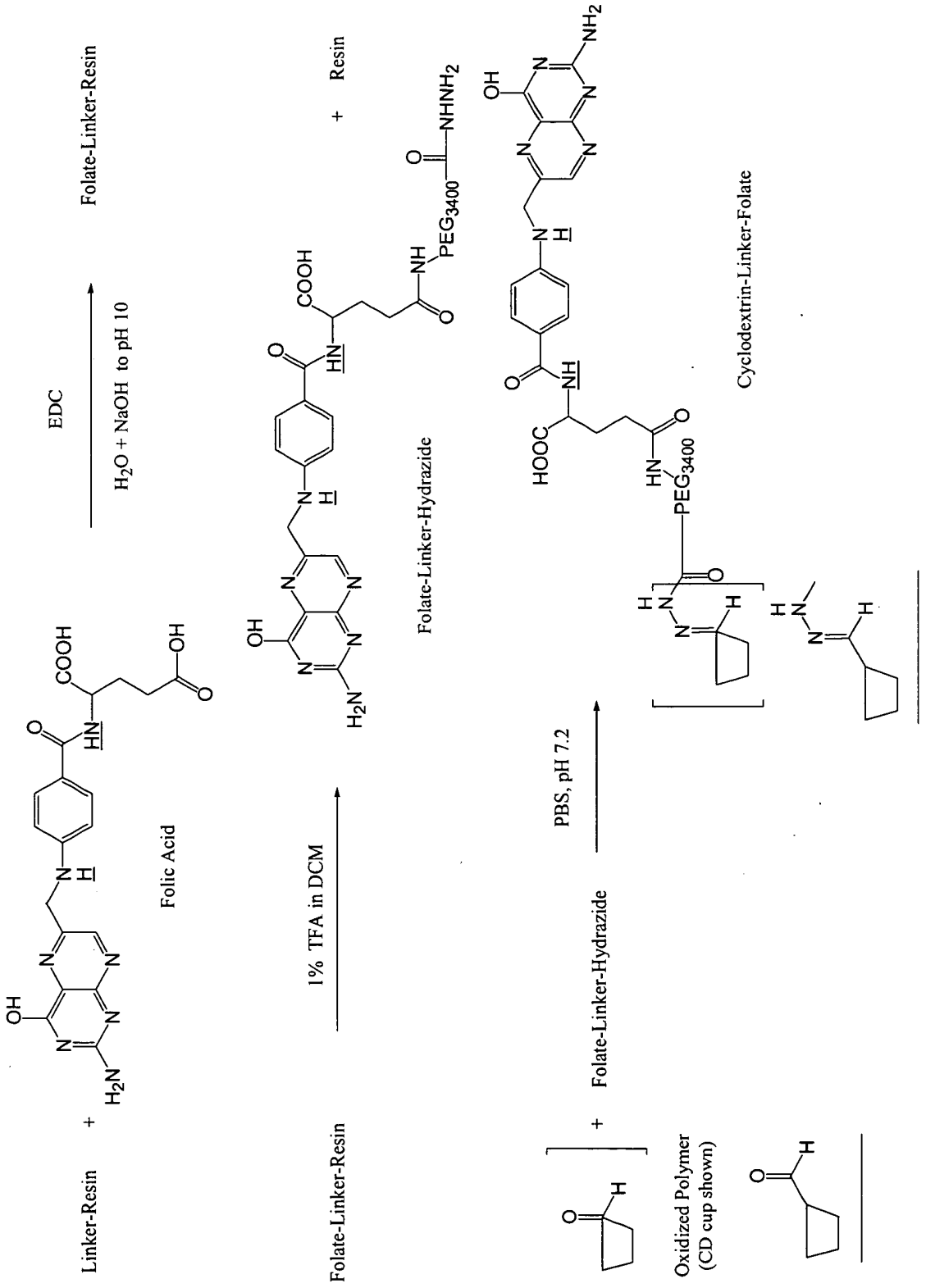
1. On pages 42, 44, and 48, please replace the schemes with the corrected schemes shown in the next three pages. In addition, in the previous amendment filed on February 19, 2002, please cancel the amendment starting "Brief Description of the figures: ...Example 19 on page 45." (page 5, lines 2-8).

~~[Brief Description of the figures:~~

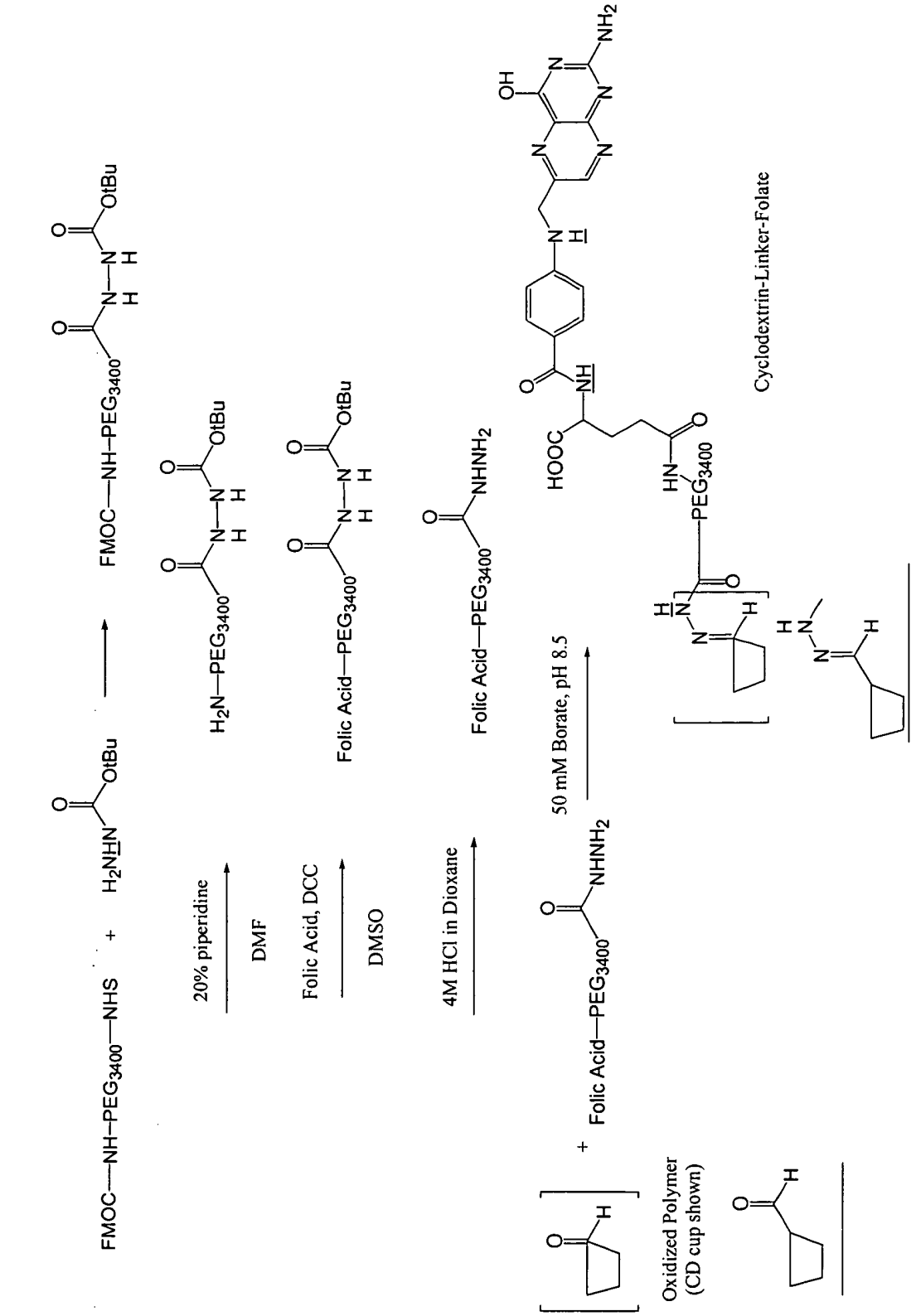
~~Figure 1 depicts the synthetic scheme for the folate ligand attachment to cyclodextrin polymer according to Example 17 on page 39.~~

~~Figure 2 depicts the synthetic scheme for the folate ligand attachment to cyclodextrin polymer according to Example 18 on page 43.~~

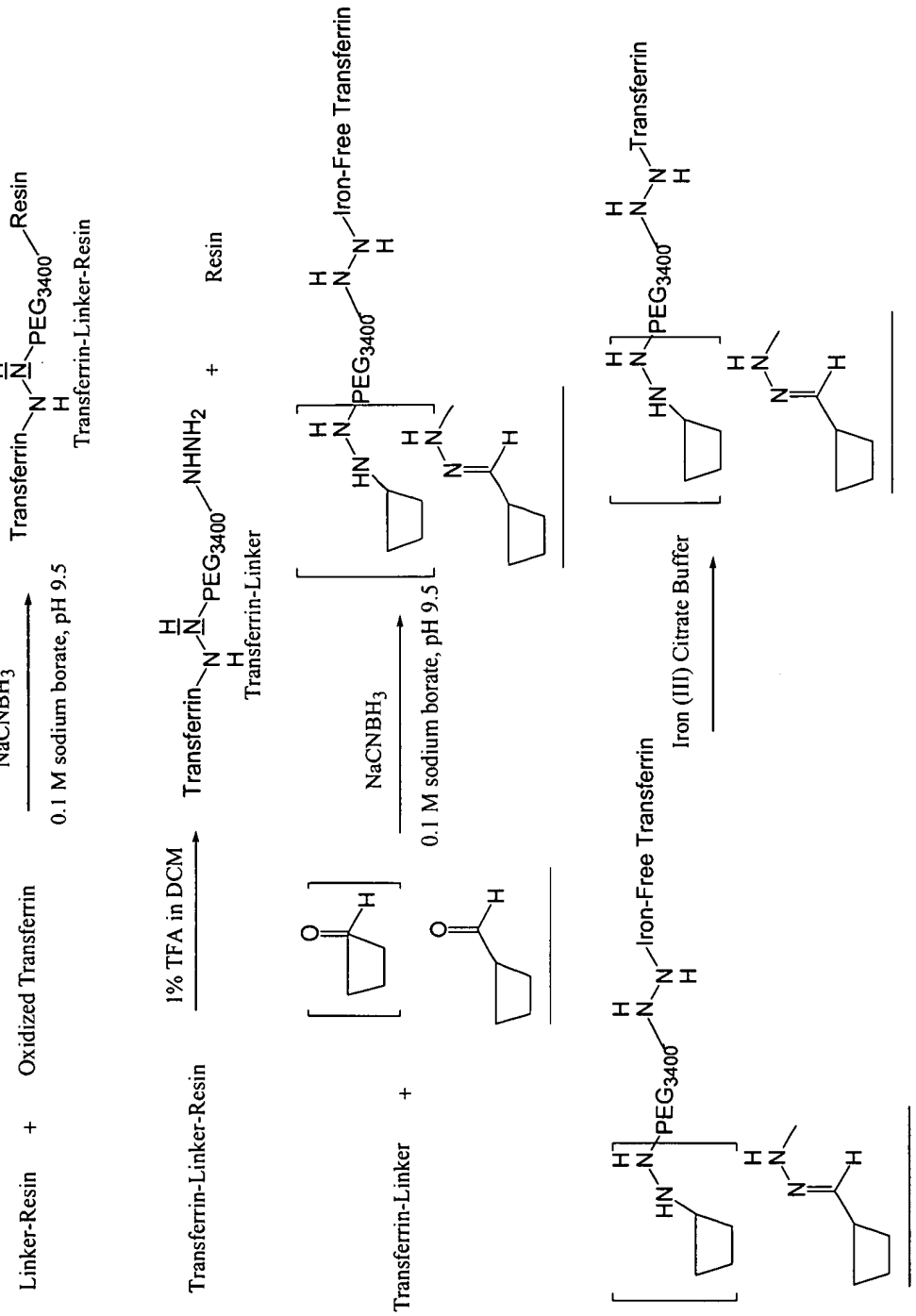
~~Figure 3 depicts the synthetic scheme for the transferrin ligand attachment to cyclodextrin polymer according to Example 19 on page 45.]~~


Linker-Resin
+
Folic Acid
EDC
H2O + NaOH to pH 10
Folate-Linker-Resin
Folate-Linker-Resin
1% TFA in DCM
+ Resin
Folate-Linker-Hydrazide
Folate-Linker-Hydrazide
PBS, pH 7.2
+
Oxidized Polymer
(CD cup shown)
Cyclodextrin-Linker-Folate

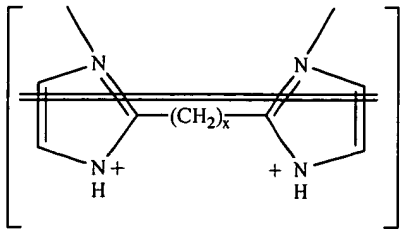
SYNTHESIS OF FOLIC ACID-PEG-HYDRAZIDE

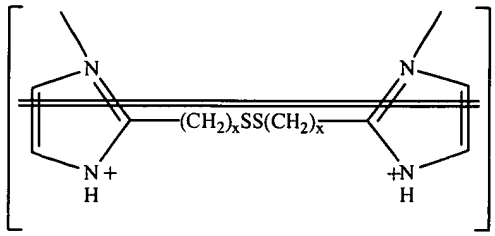


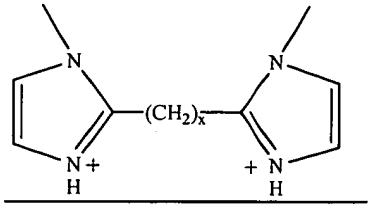
TRANSFERRIN ATTACHMENT TO CYCLODEXTRIN POLYMER

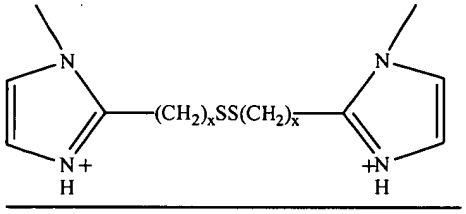


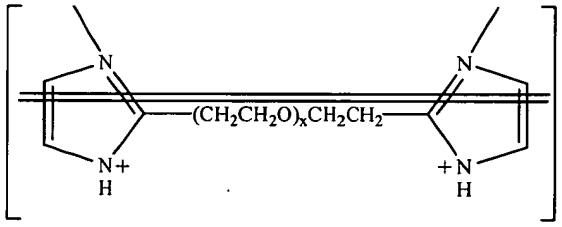
2. On page 14, please delete the three structures on the bottom of the page and replace them with the following corrected structures:

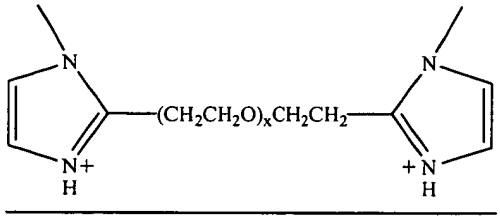




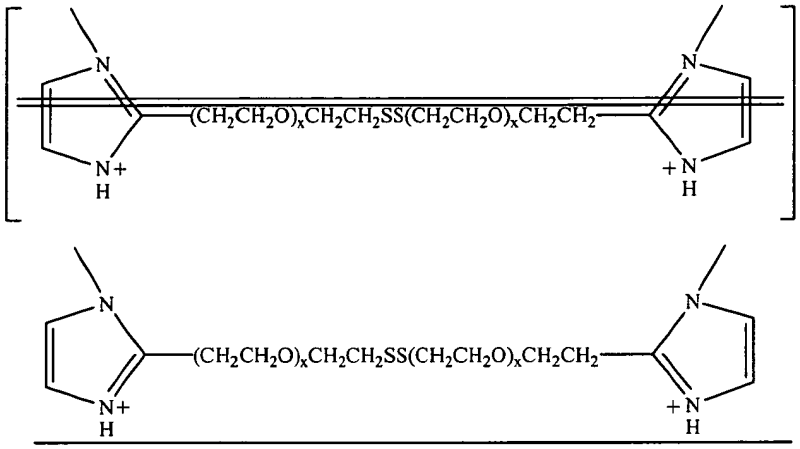








3. On page 15, please replace the structure on the top of the page with the following corrected structure:



4. On pages 53, 57, 58, 59, and 60, please delete the graphs. The graphs are replaced by Figures in the following manner:

Page Number of Original Graph	Figure
53	1A and 1B
57	2
58	3
59	4A
60	4B

Appendix B contains clean copies of Figures 1-4 with drawing labels.

5. On page 52, delete the paragraph starting at line 8, and insert the following paragraph:

BHK-21 cells were plated in 24 well plates at a cell density of 60,000 cells/well 24 hours before transfection. Plasmids encoding the luciferase gene were encapsulated by the CD-polymer as in Example 23 except copolymer **15** was replaced with copolymer **16** and that the DNA/polymer complexes successfully transfected BHK-21 cells at charge ratios of 10, 20, 30, and 40 with maximum transfection at polymer amine:DNA phosphate charge ratio of 20. Media solution containing the DNA/polymer complexes was added to cultured cells and replaced with fresh media after 24 hours of incubation at 37°C. The cells were lysed 48 hours after transfection. Appropriate substrates for the luciferase light assay were added to the cell lysate. Luciferase activity, measured in terms of light units produced, was quantified by a luminometer. The results are illustrated below. DNA/polymer complexes successfully transfected BHK-21 cells at a charge ratios of 6, 12, and 24. Cell lysate was also used to determine cell viability by the Lowry protein assay. (Lowry et al., *Journal of Biological Chemistry*, Vol. 193, 265-275 (1951)). The results are illustrated [~~below~~] in Figures 1A and 1B. Maximum toxicity was seen at a polymer amine: DNA phosphate charge ratios of 40 and 50 with 33% cell survival.

6. On page 55, please delete the paragraph starting at line 15 and insert the following paragraph:

Plasmids encoding the luciferase gene were encapsulated by the CD-polymer as in Example 23 except copolymer **15** was replaced with copolymer **16**. The DNA/polymer complexes were used to successfully transfect BHK-21 or CHO-K1 cells, each plated in 24 well plates at a cell density of 60,000 cells/well 24 hours before transfection, at various charge ratios in 10% serum

and serum-free conditions following the procedure outlined in Example 27. The cells were lysed 48 hours after transfection. Appropriate substrates for the luciferase light assay were added to the cell lysate. Luciferase activity, measured in terms of light units produced (*i.e.,* relative light units (RLU)), was quantified by a luminometer. Cell lysate was also used to determine cell viability by the Lowry protein assay. (Lowry et al., *Journal of Biological Chemistry*, Vol. 193, 265-275 (1951)). Toxicity was measured by determining total cellular protein in the wells 48 hours after transfection. The transfection and cell survival results in 10% serum and serum free media are illustrated [~~below~~] in Figures 2 and 3.

7. On page 59, please delete the paragraph starting at line 3, and insert the following paragraph:

Following the procedure of Example 32, transfection efficiency and toxicity of various non-viral vectors with BHK-21 and CHO-K1 cells were studied and compared against those achieved with DNA/copolymer **16** complexes. The BHK-21 and CHO-K1 cells were transfected at a range of charge ratios and starting cell densities for all vectors in serum-free media. The results are illustrated [~~below~~] in Figures 4A and 4B, and illustrate the optimum transfection conditions found for each vector.

8. At age 7, line 20, please insert the following description of the figures before "Detailed Description of the Invention,":

Brief Description of the Figures:

Figure 1 depicts Transfection Studies with Plasmids Encoding *Luciferase Reporting Gene*: Figure 1A, Transfection with copolymer 16; and Figure 1B Toxicity of copolymer 16 to BHK-21.

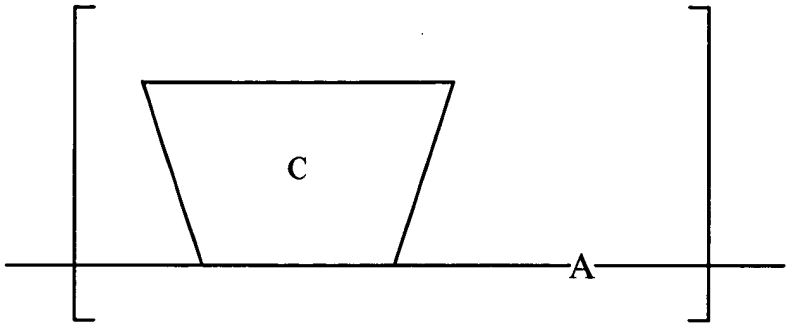
Figure 2 depicts Transfection and Toxicity of Copoloymer 16 to BHK-21.

Figure 3 depicts Transfection and Toxicity of Copolymer 16 to CHO-K1.

Figure 4 relates to Comparative Example 1 and depicts Transfection Studies with Plasmids Encoding *Luciferase Reporter Gene*: Figure 4A, Relative Light Units; and 4B Fraction Cell Survival

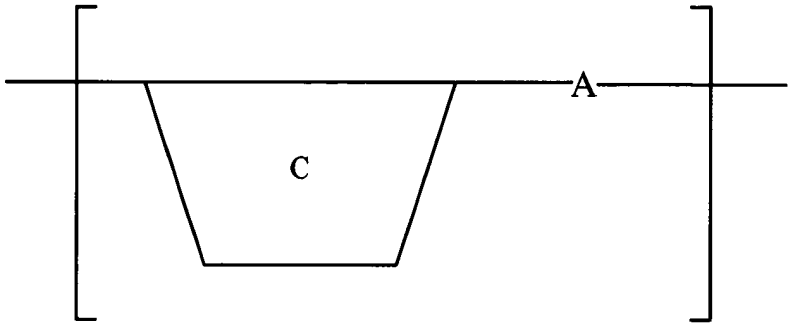
IN THE CLAIMS:

1 (Amended) A water-soluble, linear cyclodextrin copolymer comprising repeating units of formula Ia, Ib or a combination thereof:



(Ia)

and

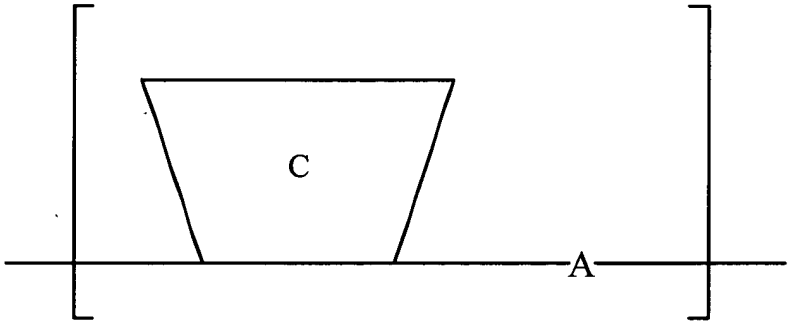


(Ib)

wherein C is a substituted or unsubstituted cyclodextrin monomer and A is a comonomer bound to cyclodextrin C.

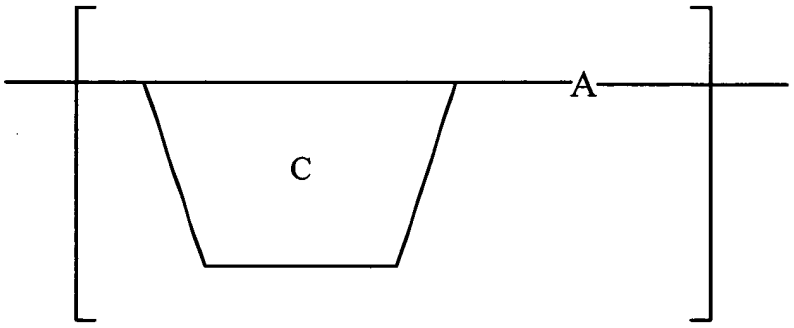
24. (Amended) A method of preparing a water-soluble, linear cyclodextrin copolymer comprising the steps of:

copolymerizing a cyclodextrin monomer precursor, where said cyclodextrin monomer precursor is disubstituted with the same or different leaving group, with a comonomer A precursor capable of displacing said leaving groups to form a linear cyclodextrin copolymer having repeating units of formula Ia and Ib, or a combination thereof:



(Ia)

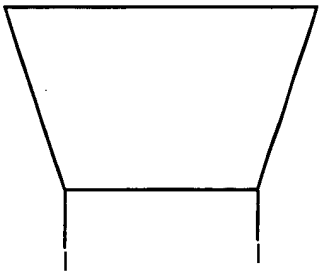
and



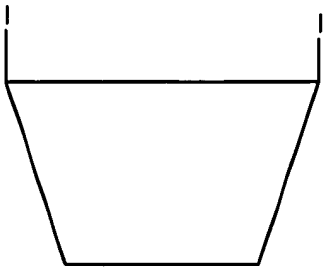
(Ib)

wherein C is a substituted or unsubstituted cyclodextrin monomer and A is a comonomer bound to cyclodextrin C.

25. (Amended) A method of preparing a water-soluble, linear cyclodextrin copolymer of claim 24, wherein said disubstituted cyclodextrin monomer precursor is a diiodinated cyclodextrin monomer precursor of formula IVa, IVb, IVc or a mixture thereof:

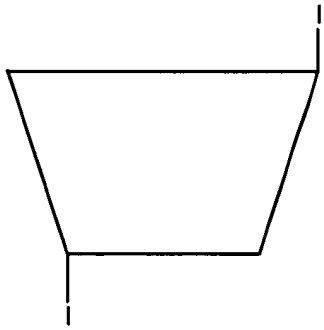


(IVa)



(IVb)

and



(IVc)